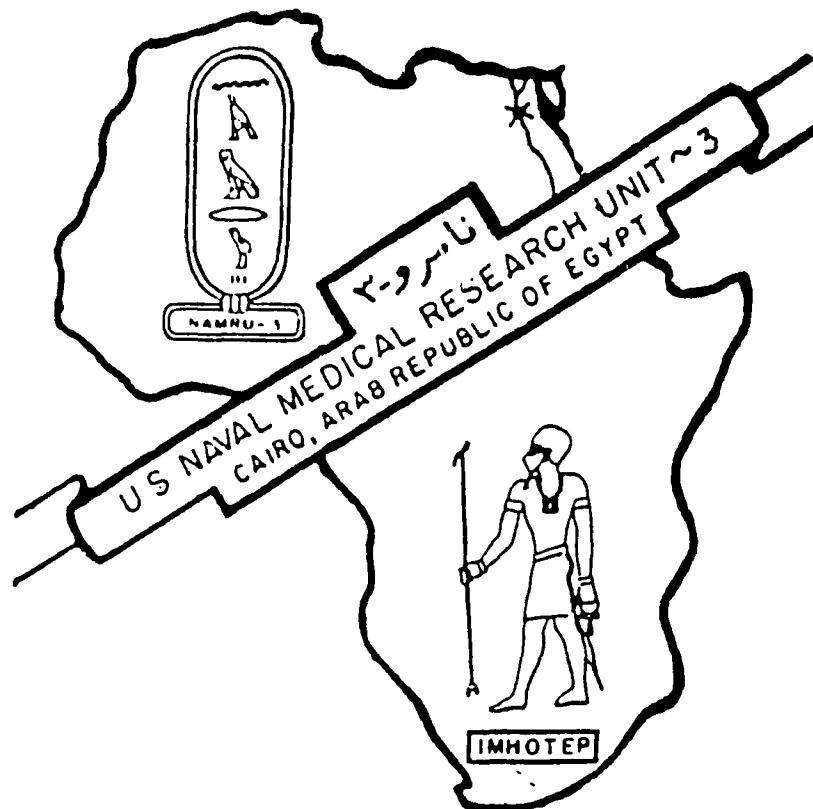


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CEFIXIME IN THE TREATMENT OF ENTERIC FEVER IN CHILDREN

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Summary: Cefixime in a dose 20 mg/kg/day, orally, divided into two doses 12 h apart for a minimum of 12 days, was administered to 50 children with proven *S. typhi* septicaemia. Forty four of the patients were infected with strains of *S. typhi* resistant to multiple antibiotics including chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole. All patients responded rapidly to treatment and were cured clinically and bacteriologically. Fever subsided within a mean of 5.3 days (range 3-8 days). Only two of the 50 patients treated relapsed during the 8 week follow-up period. No serious adverse reactions attributable to the drug were observed. Cefixime proved to be an effective oral drug in this open treatment trial and was associated with minimal side effects. It may provide a therapeutic alternative to the treatment of *Salmonella* infection with organisms multi-resistant to the standard drug regimens. Its oral formulation may provide an efficient alternative to parenteral therapy in less severely ill patients who can tolerate oral feeding.

Introduction

Salmonella typhi and *Salmonella paratyphi* organisms resistant to chloramphenicol, trimethoprim-sulfamethoxazole and ampicillin were reported from Egypt for the first time in 1989 (1). The increase in the incidence of multi-resistant strains isolated over the past few years from both Egypt and other parts of the world (2) has made it necessary to evaluate new agents that could be used safely in the treatment of these infections.

Several studies have recently shown that the quinolone group of drugs can be used successfully in the treatment of multi-resistant *S. typhi* and *S.*

paratyphi infections. However, the main drawback of the quinolone drugs is that they cannot be administered to children under 16 years of age (3). Ceftriaxone and aztreonam have both been found effective in the treatment of children and adults with enteric fever but both have to be administered parenterally (4, 5).

Cefixime, an oral third generation cephalosporin, has been shown to be highly active *in vitro* against *Salmonella*, and reports indicate its safety and efficacy in the treatment of a variety of other infections in adults and children (6, 7).

In the present study oral cefixime was used in the treatment of *Salmonella typhi* septicaemia in children. The study took place during the 10 month period from May 1991 to February 1992 at the U.S. Naval Medical Research Unit No. Three (NAMRU 3)/Abbassia Fever Hospital's Clinical Diagnosis Centre.

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Patients and methods

Children 16 years of age and younger presenting with signs and symptoms of enteric fever were enrolled in the study after informed oral consent explaining the nature of the study was obtained from their parents. Only patients who were able to tolerate oral feeding and had no clinical evidence of intestinal perforation, shock or other serious complications were included in the trial.

The 50 children with confirmed *S. typhi* septicaemia were 4–15 years old (median 11 years); 30 were males and 20 were females. They were treated with cefixime 20 mg/kg/day, orally, divided into two equal doses given 12 h apart for a minimum of 12 days.

Blood, stool and urine cultures were obtained on two successive days prior to initiation of therapy. Blood was also examined for complete blood count, Widal test, glucose, urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, bilirubin and alkaline phosphatase. All the above tests were repeated once during therapy, at the end of therapy and 1, 2 and 4 weeks after completion of therapy.

Results

All the *Salmonella* strains isolated were sensitive to cefixime, ceftriaxone, aztreonam, ciprofloxacin and norfloxacin by the Kirby Bauer disc diffusion method (8); however, only six were sensitive to chloramphenicol, trimethoprim-sulfamethoxazole or ampicillin. The clinical details of the patients are presented in Table I.

Clinical efficacy. All patients responded rapidly to treatment, with signs and symptoms rapidly controlled (Table II). The mean number of days taken for patients to become afebrile (rectal temperature below 38.5°C) was 5.3 (± 1.5 , range 3 to 8 days). The fever subsided by day 4 in 18 children, by day 5 in 16, by day 6 in 8, and by day 8 in 8 children.

Table I Clinical details of 50 children with *S. typhi* septicaemia

Clinical presentation	No. Patients (%)
Temp. above 38.5°C	43 (86)
Headache	45 (90)
Cough	18 (36)
Constipation	21 (42)
Palpable spleen	45 (90)
Palpable liver	42 (84)
Mental changes	6 (12)

Table II Mean number of days \pm standard deviation taken for symptoms/signs to respond to cefixime treatment in 50 children with *S. typhi* septicaemia

Symptom/Sign	Mean \pm s.d.
Afebrile $< 38.5^\circ\text{C}$	5.3 \pm 1.5
Headache	3.2 \pm 1.3
Constipation	1.1 \pm 1.6
Splenomegaly	3.7 \pm 1.9
Hepatomegaly	3.2 \pm 2.0
Mental changes	1.9 \pm 1.7

Bacteriological efficacy. Blood, stool and urine cultures taken during and after therapy were negative in all patients. Two patients became febrile, with signs and symptoms of enteric fever 18 and 21 days, respectively, after completion of cefixime therapy. *S. typhi* was again isolated from their blood. The sensitivity pattern of both strains was similar to that obtained prior to initiation of therapy. These two patients were re-treated with cefixime and cured.

Mild side reactions of nausea, abdominal pain and colic were observed in six of the children. No adverse effects were noted in the blood chemistry profile of any patient during or following cefixime therapy.

Discussion

This open clinical trial suggests that cefixime given orally may be a useful alternative to chloramphenicol, ampicillin, trimethoprim-sulphamethox-

azole, ceftriaxone and aztreonam in the treatment of enteric fever in children in areas where multiple antibiotic resistant strains of *S. typhi* are present.

However, several precautions should be noted with cefixime for the therapy of enteric fever. This study was limited to moderately ill children with no evidence of serious complications who were able to tolerate oral antibiotic therapy. The oral formulation facilitated nursing care and eliminated the additional requirements for the delivery of parenteral medication. Patients in our facility with underlying complications with potential multi-resistant *S. typhi* were treated with either parenteral ceftriaxone or aztreonam.

Another concern with oral cefixime therapy is the potential alteration of faecal flora. Studies in healthy adult volunteers have reported alterations in faecal flora after receiving cefixime for one to two weeks with the emergence of *Clostridium difficile* strains in some subjects (9, 10). Although no gastrointestinal complications were noted in the present study, enterocolitis due to *C. difficile* toxin must be considered as a potential complication of cefixime therapy until further clinical experience becomes available.

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